

PATENT
Attorney Docket No. AME-06381

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: William D Huse *et al.*

Serial No.: 09/982,464

Filed: 10/18/2001

Entitled: **Methods of Optimizing Antibody Variable Region
Binding Affinity**

Group No.: 1642

Examiner: Helms, L.

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Dated: September 12, 2003

By


Christopher Collins

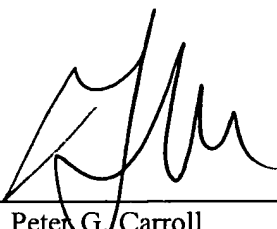
Sir or Madam:

Enclosed please find an Information Disclosure Statement and Form PTO-1449, including copies of the references contained thereon, for filing in the U.S. Patent and Trademark Office.

A check for \$180.00 is also enclosed pursuant to 37 C.F.R. § 1.17(p) for filing this Information Disclosure Statement after three months as set forth in 37 C.F.R. § 1.97(c).

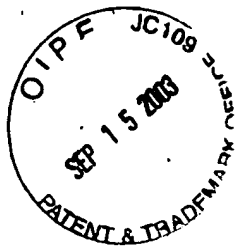
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Dated: September 12, 2003



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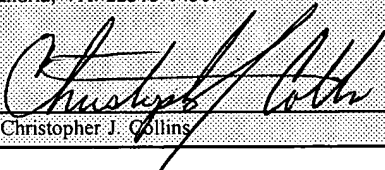
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Dated: <u>September 12, 2003</u>	By:  Christopher J. Collins

Sir:

The citations listed below, copies attached, may be material to the examination of the above-identified application, and are therefore submitted in compliance with the duty of disclosure defined in 37 C.F.R. §§ 1.56 and 1.97. The Examiner is requested to make these citations of official record in this application.

The following printed publications are referred to in the body of the specification. The publications with an asterisk (*) designate that hard copies were submitted with the IDS filed on 6/02/00 in the parent case 09/434,870 filed 11/04/99. Please make these publications of record in the instant application:

- U.S. Patent No. 5,223,409* to Ladner *et al.*;
- U.S. Patent No. 5,264,563* to Huse;
- U.S. Patent No. 5,403,484 to Ladner *et al.*;
- U.S. Patent No. 5,523,388 to Huse;
- U.S. Patent No. 5,871,974 to Huse;

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- Ansubel *et al.*, Current Protocols in Molecular Biology, John Wiley and Sons, Baltimore, MD (1998)¹;
- Chothia *et al.*, "Conformations of immunoglobulin hypervariable regions," *Nature* 342:877-883 (1989)*;
- Chothia *et al.*, "Canonical structures for the hypervariable regions of immunoglobulins," *J. Mol. Biol.* 196:901-917 (1987)*;
- Day, E.D., Advanced Immunochemistry, Second Ed., Wiley-Liss, Inc., New York, NY (1990)²;
- Durie *et al.*, "Antibody to the Ligand of CD40, gp39, Blocks the Occurrence of the Acute and Chronic Forms of Graft-vs-Host Disease," *J Clin Invest* 94:1333-1338 (1994);
- Foy *et al.*, "Immune Regulation by CD40 and its Ligand GP39," *Annu Rev Immunol* 14:591-617 (1996);
- Francisco *et al.*, "In Vivo Efficacy and Toxicity of a single-Chain Immunotoxin Targeted to CD40," *Blood* 89:4493-4500 (1997);
- Francisco *et al.*, "Activity of a single-Chain Immunotoxin that Selectively Kills Lymphoma and other B-Lineage Cells expressing the CD40 Antigen," *Cancer Res* 55:3099-3104 (1995);
- Glaser *et al.*, "Antibody engineering by codon-based mutagenesis in a filamentous phage vector system," *J. Immunology* 149:3903-3913 (1992)*;
- Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, New York (1989)³;
- Harris & Bajorath, "Profiles for the analysis of immunoglobulin sequences: Comparison of V gene subgroups," *Prot Sci* 4:306-310 (1995);

¹ This is a general text that was cited in the specification without direction to any specific page, applicants have not included any excerpts with this IDS.

² This is a general text that was cited in the specification without direction to any specific page, applicants have not included any excerpts with this IDS.

³ This is a general text that was cited in the specification without direction to any specific page, applicants have not included any excerpts with this IDS.

- Huston *et al.*, "Antigen Recognition and Targeted Delivery by the Single-Chain Fv," *Cell Biophysics*, 22:189-224 (1993);
- Jönsson and Malmquist, "Real Time Biospecific Interaction Analysis," *Advances in Biosensors*, 2:291-336 (1992);
- Kabat *et al.*, *Sequences of protein of immunological interest.*, (5th Ed) Washington DC: United States Department of Health and Human Services (1991)*;
- Kabat *et al.*, "Unusual distributions of amino acids in complementarity determining (hypervariable) segments of heavy and light chains of immunoglobulins and their possible roles in specificity of antibody combining sites," *J. Biol. Chem.* 252, 6609-6616 (1977)*;
- Kristensson *et al.*, "Humanization of a murine antibody against cryptococcus neoformans polysaccharide using a novel approach," *Vaccines* 95, pp. 39-43 Cold Springs Harbor Laboratory Press, Cold Spring Harbor, NY (1995)*;
- Kunkel, "Rapid and Efficient site-specific mutagenesis without phenotypic selection," *Proc Natl. Acad Sci USA* 82:488-492 (1985);
- MacCallum *et al.*, "Antibody-antigen interactions: contact analysis and binding site topography," *J. Mol. Biol.* 262:732-745 (1996)*;
- Mach *et al.*, "Reduction of atherosclerosis in mice by inhibition of CD40 signalling," *Nature* 394:200-203 (1998);
- Molec. Biology and Biotechnology: A Comprehensive Desk Reference (Myers, R.A. (ed.), New York: VCH Publisher, Inc.)⁴;
- Padlan, "A possible procedure for reducing the immunogenicity of antibody variable domains while preserving their ligand-binding properties," *Mol Immunol* 28:489-498 (1991)*;
- Padlan, "Anatomy of the antibody molecule," *Mol Immunol* 31:169-217 (1994)*;
- Plückthun and Skerra, "Expression of Functional Antibody Fv and Fab Fragments in *Escherichia coli*," *Meth. Enzymol.*, 178:497-515 (1989);

⁴ This is a general text that was cited in the specification without direction to any specific page, applicants have not included any excerpts with this IDS.

- Rosok *et al.*, "A combinatorial library strategy for the rapid humanization of anticarcinoma BR96 Fab," *J Biol Chem* 271:22611-22618 (1996)*;
- Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, New York (1992)⁵;
- Schreiber & Fersht, "Energetics of protein-protein interactions: Analysis of the barnase-barstar interface by single mutations and double mutant cycles," *J Mol Biol* 248:478-486 (1995)*;
- Stamenkovic *et al.*, "A B-lymphocyte activation molecule related to the nerve growth factor receptor and induced by cytokines in carcinomas," *EMBO J* 8(5): 1403-1410 (1989);
- Studnicka *et al.*, "Human-engineered monoclonal antibodies retain full specific binding activity by preserving non-CDR complementarity modulating residues," *Protein Eng* 7:805-814 (1994)*;
- Uckun *et al.*, "Temporal Association of CD40 Antigen Expression with Discrete Stages of Human B-Cell Ontogeny and the Efficacy of Anti-CD40 Immunotoxins Against Clonogenic B-Lineage Acute Lymphoblastic Leukemia as Well as B-Lineage Non-Hodgkin's Lymphoma Cells," *Blood* 76(12):2449-2456 (1990);
- Watkins *et al.*, "Discovery of human antibodies to cell surface antigens by capture lift screening of phage-expressed antibody libraries," *Anal Biochem* 256:169-177 (1998)*;
- Watkins *et. al.*, "Determination of the relative affinities of antibody fragments expressed in Escherichia coli by enzyme-linked immunosorbent assay," *Anal Biochem* 253:37-45 (1997)*;
- Wilson & Stanfield, *Curr Opin Struct Biol* 3:113-118 (1993)⁶; and
- Wu *et al.*, "Stepwise in vitro affinity maturation of Vitaxin, and $\alpha_v\beta_3$ -specific humanized mAb," *Proc. Natl. Acad. Sci. USA*, 95:6037-6042 (1998)*.

⁵ This is a general text that was cited in the specification without direction to any specific page, applicants have not included any excerpts with this IDS.

⁶ We are unable to located this reference, if the examiner request a copy we will try to obtain it.

Applicants have become aware of the following printed publications which may be material to the examination of this application.

The following publications with an asterisk (*) designate that hard copies were submitted with the IDS filed on 6/02/00 in the parent case 09/434,870 filed 11/04/99. Please make these publications of record in the instant application:

- U.S. Patent No.: 5,225,539* to Winter *et al.*.
- U.S. Patent No.: 5,585,089* to Queen *et al.*.
- U.S. Patent No.: 5,693,762* to Queen *et al.*.
- U.S. Patent No.: 5,723,323* to Kauffman *et al.*.
- U.S. Patent No.: 5,814,476* to Kauffman *et al.*.
- U.S. Patent No.: 5,817,483* to Kauffman *et al.*.
- U.S. Patent No.: 5,824,514* to Kauffman *et al.*.
- U.S. Patent No.: 5,976,862* to Kauffman *et al.*.
- EPO Patent 0 451 216 B1*.
- EPO Patent 0 682 040 B1*.
- EPO Patent 0 939 127 A2*.
- Foote and Winter, "Antibody framework residues affecting the conformation of the hypervariable loops," *J Mol Biol* 224:487-499 (1992)*.
- Jones *et al.*, "Replacing the complementarity-determining regions in a human antibody with those from a mouse," *Nature* 321:522-525 (1986)*.
- Rader *et al.*, "A phage display approach for rapid antibody humanization: Designed combinatorial V gene libraries," *Proc Natl Acad Sci USA* 95:8910-8915 (1998)*.
- Riechmann *et al.*, "Reshaping human antibodies for therapy," *Nature* 332:323-327 (1988)*.
- Schier *et al.*, "Isolation of picomolar affinity anti-c-erbB-2 single-chain Fv by molecular evolution of the complementarity determining regions in the center of the antibody binding site," *J Mol Biol* 263:551-567 (1996)*.
- Singer *et al.*, "Optimal humanization of 1B4, an anti-CD 18 murine monoclonal antibody, is achieved by correct choice of human V-region framework sequences," *J Immunol* 150:2844-2857 (1993)*.

- Thompson *et al.*, "Affinity maturation of a high-affinity human monoclonal antibody against the third hypervariable loop of human immunodeficiency virus: Use of phage display to improve affinity and broaden strain reactivity," *J Mol Biol* 256:77-88 (1996)*.
- Yelton *et al.*, "Affinity maturation of the BR96 anti-carcinoma antibody by codon-based mutagenesis," *J Immunol* 155:1994-2004 (1995)*.

The following publications with an asterisk (*) designate that hard copies were submitted with a Supplemental IDS filed on 4/25/01 in the parent case 09/434,870 filed 11/04/99. Please make these publications of record in the instant application:

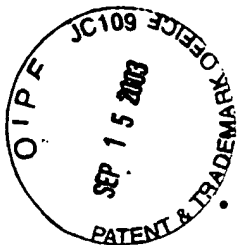
- U.S. Patent No. 6,096,551 to Barbas *et al.**
- EPO 0 519 596 A1*
- CA 2,125,240 A1*, and
- Irving *et al.*, "Affinity maturation of recombinant antibodies using *E. coli* mutator cells," *Immunotechnology* 2:127-143 (1996)*.

The following publications with an asterisk (*) designate that hard copies were submitted with a Supplemental IDS filed on 5/01/02 in the parent case 09/434,870 filed 11/04/99. Please make these publications of record in the instant application:

- U.S. Patent No.: 5,977,322 to Marks *et al.**
- U.S. Patent No.: 6,312,693 to Aruffo *et al.**
- PCT WO 99/42075 publication date 26.08.99*.

The following publications with an asterisk (*) designate that hard copies were provided by the examiner cited on an 892 notice dated 3/15/01 in the parent case 09/434,870 filed 11/04/99. Please make these publications of record in the instant application:

- Baca *et al.*, "Antibody humanization using monovalent phage display," *J. Biol Chem* 272:10678-84 (1997)*.
- Baca *et al.*, "Phage display of a catalytic antibody to optimize affinity for transition-state analog binding," *Proc Natl Acad Sci USA* 94:10063-10068 (1997)*.
- Amit *et al.*, "Three-Dimensional Structure of an Antigen-Antibody Complex at 2.8 Å Resolution," *Science* 233:747-753 (1986)*, and



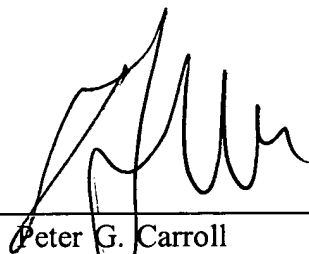
Rudikoff *et al.*, "Single amino acid substitution altering antigen-binding specificity," *Proc Natl Acad Sci USA* 79:1979-1983 (1982)*.

The following publication was cited in an International Search Report in the parent case 09/434,870 filed 11/04/99. This publication is provided.

- Herren *et al.*, "Humanization of a murine monoclonal antibody by simultaneous optimization of framework and CDR residues," *J Molecular Biology* 294:151-162 (1999).

This Information Disclosure Statement under 37 C.F.R. §§ 1.56 and 1.97 is not to be construed as a representation that a search has been made, that additional information material to the examination of this application does not exist, or that any one or more of these citations constitutes prior art.

Dated: September 12, 2003



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FORM PTO-149
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Attorney Docket No.: AME-06381

Serial No.: 09/28,464

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use Several Sheets if Necessary)

Applicant: William D Huse *et al.*

Filing Date: 10/18/2001

Group Art Unit: 1642

(37 CFR § 1.98(b))

U.S. PATENT DOCUMENTS

Examiner Initials	Cite No.	Patent / Patent Number	Issue Date	Applicant / Patentee	Class	Subclass	Filing Date
	1	5,223,409	6/29/93	Ladner <i>et al.</i>			3/1/91
	2	5,225,539	10/25/91	Winter			10/25/91
	3	5,264,563	11/23/93	Huse			12/14/92
	4	5,403,484	4/4/95	Ladner <i>et al.</i>			1/26/93
	5	5,523,388	6/4/96	Huse			2/27/95
	6	5,585,089	12/17/96	Queen <i>et al.</i>			6/7/95
	7	5,693,762	12/2/97	Queen <i>et al.</i>			6/7/95
	8	5,723,323	3/3/98	Kauffman <i>et al.</i>			12/2/94
	9	5,814,476	9/29/98	Kauffman <i>et al.</i>			6/5/95
	10	5,817,483	10/6/98	Kauffman <i>et al.</i>			6/5/95
	11	5,824,514	10/20/98	Kauffman <i>et al.</i>			6/5/95
	12	5,871,974	2/16/99	Huse			12/2/94
	13	5,976,862	11/2/99	Kauffman <i>et al.</i>			6/5/95
	14	5,977,322	11/2/99	Marks <i>et al.</i>			6/13/96
	15	6,096,551	8/1/00	Barbas <i>et al.</i>			9/16/97
	16	6,312,693	11/6/01	Aruffo <i>et al.</i>			2/10/99

FOREIGN PATENTS OR PUBLISHED FOREIGN PATENT APPLICATIONS

		Document Number	Publication Date	Country / Patent Office	Class	Subclass	Translation	
							Yes	No
	17	0 451 216 B1	10/16/91	EPO				
	18	0 682 040 B1	11/15/95	EPO				
	19	0 939 127 A2	9/01/99	EPO				
	20	0 519 596 A1	5/12/92	EPO				
	21	WO 99/42075	26.08.99	PCT				
	22	2,125,240 A1	12/7/95	CA				

OTHER DOCUMENTS (Including Author, Title, Date, Relevant Pages, Place of Publication)

	23	Amit <i>et al.</i> , "Three-Dimensional Structure of an Antigen-Antibody Complex at 2.8 A Resolution," <i>Science</i> 233:747-753 (1986)
	24	Baca <i>et al.</i> , "Antibody humanization using monovalent phage display," <i>J. Biol Chem</i> 272:10678-84 (1997)
	25	Baca <i>et al.</i> , "Phage display of a catalytic antibody to optimize affinity for transition-state analog binding," <i>Proc Natl Acad Sci USA</i> 94:10063-10068 (1997)
	26	Chothia <i>et al.</i> , "Conformations of immunoglobulin hypervariable regions," <i>Nature</i> 342:877-883 (1989)

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Date Considered:

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Initial citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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Attorney Docket No.: AME-06381

Serial No.: 09/982,298

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(37 CFR § 1.98(a))

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| 27 | Chothia <i>et al.</i> , "Canonical structures for the hypervariable regions of immunoglobulins," <i>J. Mol. Biol.</i> 196:901-917 (1987) |
| 28 | Durie <i>et al.</i> , "Antibody to the Ligand of CD40, gp39, Blocks the Occurrence of the Acute and Chronic Forms of Graft-vs-Host Disease," <i>J Clin Invest</i> 94:1333-1338 (1994) |
| 29 | Foote and Winter, "Antibody framework residues affecting the conformation of the hypervariable loops," <i>J Mol Biol</i> 224:487-499 (1992) |
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| 32 | Francisco <i>et al.</i> , "Activity of a single-Chain Immunotoxin that Selectively Kills Lymphoma and other B-Lineage Cells expressing the CD40 Antigen," <i>Cancer Res</i> 55:3099-3104 (1995) |
| 33 | Glaser <i>et al.</i> , "Antibody engineering by codon-based mutagenesis in a filamentous phage vector system," <i>J. Immunology</i> 149:3903-3913 (1992) |
| 34 | Harris & Bajorath, "Profiles for the analysis of immunoglobulin sequences: Comparison of V gene subgroups," <i>Prot Sci</i> 4:306-310 (1995) |
| 35 | Herren <i>et al.</i> , "Humanization of a murine monoclonal antibody by simultaneous optimization of framework and CDR residues," <i>J Molecular Biology</i> 294:151-162 (1999) |
| 36 | Huston <i>et al.</i> , "Antigen Recognition and Targeted Delivery by the Single-Chain Fv," <i>Cell Biophysics</i> , 22:189-224 (1993) |
| 37 | Irving <i>et al.</i> , "Affinity maturation of recombinant antibodies using E. coli mutator cells," <i>Immunotechnology</i> 2:127-143 (1996) |
| 38 | Jones <i>et al.</i> , "Replacing the complementarity-determining regions in a human antibody with those from a mouse," <i>Nature</i> 321:522-525 (1986) |
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| 42 | Kristensson <i>et al.</i> , "Humanization of a murine antibody against cryptococcus neoformans polysaccharide using a novel approach," <i>Vaccines</i> 95, pp. 39-43 Cold Springs Harbor Laboratory Press, Cold Spring Harbor, NY (1995) |
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| 44 | MacCallum <i>et al.</i> , "Antibody-antigen interactions: contact analysis and binding site topography," <i>J. Mol. Biol.</i> 262:732-745 (1996) |
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| 47 | Padlan, "Anatomy of the antibody molecule," <i>Mol Immunol</i> 31:169-217 (1994) |
| 48 | Plückthun and Skerra, "Expression of Functional Antibody Fv and Fab Fragments in <i>Escherichia coli</i> ," <i>Meth. Enzymol.</i> , 178:497-515 (1989) |
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| 51 | Rosok <i>et al.</i> , "A combinatorial library strategy for the rapid humanization of anticarcinoma BR96 Fab," <i>J Biol Chem</i> 271:22611-22618 (1996) |
| 52 | Rudikoff <i>et al.</i> , "Single amino acid substitution altering antigen-binding specificity," <i>Proc Natl Acad Sci USA</i> 79:1979-1983 (1982) |
| 53 | Schier <i>et al.</i> , "Isolation of picomolar affinity anti-c-erbB-2 single-chain Fv by molecular evolution of the complementarity determining regions in the center of the antibody binding site," <i>J Mol Biol</i> 263:551-567 (1996) |

Examiner:

Date Considered:

EXAMINER:

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FORM PTO-1449
(Modified)U.S. Department of Commerce
Patent and Trademark Office

Attorney Docket No.: AME-06381

Serial No.: 09/983,466

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Use Several Sheets If Necessary)

(37 CFR § 1.98(b))

Applicant: William D Huse *et al.*

Filing Date: 10/18/2001

Group Art Unit: 1642

OTHER DOCUMENTS (Including Author, Title, Date, Relevant Pages, Place of Publication)

54	Schreibner & Fersht, "Energetics of protein-protein interactions: Analysis of the barnase-barstar interface by single mutations and double mutant cycles," <i>J Mol Biol</i> 248:478-486 (1995)
55	Singer <i>et al.</i> , "Optimal humanization of 1B4, an anti-CD 18 murine monoclonal antibody, is achieved by correct choice of human V-region framework sequences," <i>J Immunol</i> 150:2844-2857 (1993)
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57	Studnicka <i>et al.</i> , "Human-engineered monoclonal antibodies retain full specific binding activity by preserving non-CDR complementarity modulating residues," <i>Protein Eng</i> 7:805-814 (1994)
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59	Thompson <i>et al.</i> , "Affinity maturation of a high-affinity human monoclonal antibody against the third hypervariable loop of human immunodeficiency virus: Use of phage display to improve affinity and broaden strain reactivity," <i>J Mol Biol</i> 256:77-88 (1996)
60	Uckun <i>et al.</i> , "Temporal Association of CD40 Antigen Expression with Discrete Stages of Human B-Cell Ontogeny and the Efficacy of Anti-CD40 Immunotoxins Against Clonogenic B-Lineage Acute Lymphoblastic Leukemia as Well as B-Lineage Non-Hodgkin's Lymphoma Cells," <i>Blood</i> 76(12):2449-2456 (1990)
61	Watkins <i>et al.</i> , "Discovery of human antibodies to cell surface antigens by capture lift screening of phage-expressed antibody libraries," <i>Anal Biochem</i> 256:169-177 (1998)
62	Watkins <i>et al.</i> , "Determination of the relative affinities of antibody fragments expressed in <i>Escherichia coli</i> by enzyme-linked immunosorbent assay," <i>Anal Biochem</i> 253:37-45 (1997)
63	Wu <i>et al.</i> , "Stepwise in vitro affinity maturation of Vitaxin, and $\alpha\beta_3$ -specific humanized mAb," <i>Proc. Natl. Acad. Sci. USA</i> , 95:6037-6042 (1998)
64	Yelton <i>et al.</i> , "Affinity maturation of the BR96 anti-carcinoma antibody by codon-based mutagenesis," <i>J Immunol</i> 155:1994-2004 (1995)
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Examiner:

Date Considered:

EXAMINER: Initial citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.